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INTERACTION PROFILE FOR: CHLORPYRIFOS, LEAD, MERCURY, AND METHYLMERCURY

Prepared by:

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Agency for Toxic Substances and Disease Registry

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Comment Period Ends: March 31, 2005

PREFACE

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) mandates that the Agency for Toxic Substances and Disease Registry (ATSDR) shall assess whether adequate information on health effects is available for the priority hazardous substances. Where such information is not available or under development, ATSDR shall, in cooperation with the National Toxicology Program (NTP), initiate a program of research to determine these health effects. The Act further directs that where feasible, ATSDR shall develop methods to determine the health effects of substances in combination with other substances with which they are commonly found. The Food Quality Protection Act (FQPA) of 1996 requires that factors to be considered in establishing, modifying, or revoking tolerances for pesticide chemical residues shall include the available information concerning the cumulative effects of substances that have a common mechanism of toxicity, and combined exposure levels to the substance and other related substances. The FQPA requires that the Administrator of the Environmental Protection Agency (EPA) consult with the Secretary of the Department of Health and Human Services (which includes ATSDR) in implementing some of the provisions of the act.

To carry out these legislative mandates, ATSDR's Division of Toxicology (DT) has developed and coordinated a mixtures program that includes trend analysis to identify the mixtures most often found in environmental media, *in vivo* and *in vitro* toxicological testing of mixtures, quantitative modeling of joint action, and methodological development for assessment of joint toxicity. These efforts are interrelated. For example, the trend analysis suggests mixtures of concern for which assessments need to be conducted. If data are not available, further research is recommended. The data thus generated often contribute to the design, calibration or validation of the methodology. This pragmatic approach allows identification of pertinent issues and their resolution as well as enhancement of our understanding of the mechanisms of joint toxic action. All the information obtained is thus used to enhance existing or developing methods to assess the joint toxic action of environmental chemicals. Over a number of years, ATSDR scientists in collaboration with mixtures risk assessors and laboratory scientists have developed approaches for the assessment of the joint toxic action of chemical mixtures. As part of the mixtures program a series of documents, Interaction Profiles, are being developed for certain priority mixtures that are of special concern to ATSDR.

The purpose of an Interaction Profile is to evaluate data on the toxicology of the "whole" priority mixture (if available) and on the joint toxic action of the chemicals in the mixture in order to recommend approaches for the exposure-based assessment of the potential hazard to public health. Joint toxic action includes additivity and interactions. A weight-of-evidence approach is commonly used in these documents to evaluate the influence of interactions in the overall toxicity of the mixture. The weight-of-evidence evaluations are qualitative in nature, although ATSDR recognizes that observations of toxicological interactions depend greatly on exposure doses and that some interactions appear to have thresholds. Thus, the interactions are evaluated in a qualitative manner to provide a sense of what influence the interactions may have when they do occur.

The public comment period ends March 31, 2005. Comments should be sent to:

Agency for Toxic Substances and Disease Registry
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PEER REVIEW

A peer review panel was assembled for this profile. The panel consisted of the following members:

1. Christopher J. Borgert, Ph.D., Applied Pharmacology and Toxicology, Inc., Consulting & Research Services, Gainesville, FL
2. Kannan Krishnan, Ph.D., Human Toxicology Research Group, University of Montreal, Montreal, PQ, Canada
3. Harihara Mehendale, Ph.D., Department of Toxicology, University of Louisiana, Monroe, LA , U.S.A.

All reviewers were selected in conformity with the conditions for peer review specified in CERCLA Section 104(I)(13).

Scientists from ATSDR have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

SUMMARY

Chlorpyrifos, lead, and mercury/methylmercury were chosen as the subject for this interaction profile because of the likelihood of co-exposure and because of concerns about neurological effects in children co-exposed to these chemicals. Chlorpyrifos is an organophosphorus insecticide widely used for agricultural and indoor and outdoor residential applications in the United States. Its use, however, is being phased out. Mercury (metallic and inorganic) and lead are released to the environment from hazardous waste sites and from mining, smelting, and industrial activities. Metallic and inorganic mercury can be transformed by microorganisms into methylmercury, which bioaccumulates in the food chain. For the general population, and particularly for subsistence fishers and hunters, the most important pathway of exposure to mercury is ingestion of methylmercury in foods. Fish (including tuna, a food commonly eaten by children), other seafood, and marine mammals contain the highest concentrations. Lead, present in the environment primarily as divalent lead compounds, also contaminates the environment due to its release from mining and from deteriorating lead paint and its historical use in gasoline.

No pertinent health effects data or physiologically-based pharmacokinetic (PBPK) models were located for the complete mixture. Therefore, as recommended by ATSDR (2001a) guidance, the exposure-based screening assessment of potential health hazards for this mixture depends on an evaluation of the health effects data and mechanistic data for the individual components and on the joint toxic action and mechanistic data for various combinations of the components. This profile discusses and evaluates the evidence for joint toxic action among binary mixtures of these chemicals. The profile also recommends how to incorporate concerns regarding possible interactions or additivity into public health assessments of people who may be exposed to mixtures of these chemicals.

The primary effect of concern for this mixture is neurological, and the sub-population of concern is children. Neurological effects are the critical effects for chlorpyrifos, lead, and methylmercury, and children are known (for lead and methylmercury) or predicted on the basis of animal studies (for chlorpyrifos) to be more sensitive than adults. Although metallic mercury causes neurological effects when inhaled, this route is of concern primarily for occupational exposure. Children may be exposed to metallic mercury if they play with it after finding it in abandoned warehouses or taking it from school laboratories. Broken thermometers and some electrical switches are other sources of metallic mercury. Some absorption of metallic mercury occurs from dental amalgam fillings, probably following volatilization from the fillings. Clear evidence of adverse effects from this pathway of exposure is lacking, as are joint action studies with the other components of this mixture, so this form of mercury is

not considered further in the interaction profile. The critical effect of inorganic mercury is on the kidney, which is not a sensitive target organ for the other components of the mixture.

Recommendations for screening this mixture for potential hazards to public health include estimating the hazard quotients (ratios of exposures to health guidance values) for the individual components. If only one or if none of the components has a hazard quotient that is at least 0.1, no further assessment of the *joint toxic action* is needed because additivity and/or interactions are unlikely to result in significant health hazard. If the hazard quotients for two or more of the mixture components equal or exceed 0.1, the following procedures are recommended. To screen this mixture for potential neurological health hazard, an endpoint-specific hazard index for neurological effects should be estimated for chlorpyrifos, lead, and methylmercury. The weight-of-evidence (WOE) analysis for interactions among these components indicates that joint toxic action is primarily less than additive or additive and, therefore, does not increase the concern for potential health hazard above that indicated by the hazard index. This diminishes the concern for hazard indexes only slightly above one. Confidence in these WOE analyses ranges from medium to medium-low. A separate hazard quotient is recommended to screen for the renal toxicity of inorganic mercury. The WOE analysis concluded that the influence on the renal toxicity of inorganic mercury by chlorpyrifos may be less than additive and by lead may be greater than additive, but confidence in these conclusions was low and, thus, they have little impact on the assessment of potential hazards.

If the neurological hazard index for chlorpyrifos, lead, and methylmercury is significantly greater than 1, or if the hazard quotient for inorganic mercury is greater than 1, then further evaluation is needed (ATSDR 2001a), using biomedical judgment and community-specific health outcome data. Community health concerns should be considered in further evaluations (ATSDR 1992).

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ACGIH	American Conference of Governmental Industrial Hygienists
ALA	aminolevulinic acid
ALAD	aminolevulinic acid dehydratase
ALAS	delta-aminolevulinic acid synthetase
ATSDR	Agency for Toxic Substances and Disease Registry
BINWOE	binary weight-of-evidence
BUN	blood urea nitrogen
CAS	Chemical Abstracts Service
CDC	Centers for Disease Control and Prevention
CERCLA	Comprehensive Environmental Response, Compensation, and Recovery Act
Cpf	chlorpyrifos
DT	Division of Toxicology
EPA	Environmental Protection Agency
FAO	Food and Agriculture Organization
FQPA	Food Quality Protection Act
GABA	gamma-aminobutyric acid
Hg	mercury
HI	hazard index
IARC	International Agency for Research on Cancer
IEUBK	Integrated Exposure Uptake Biokinetic
ip	intraperitoneal
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
iv	intravenous
kg	kilogram
L	liter
LC_{50}	median lethal concentration (produces desired effect in 50% of the population)
LD_{50}	median lethal dose (produces desired effect in 50% of the population)
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
MeHg	methylmercury
mg	milligram
MRL	Minimal Risk Level
MTD	maximum threshold dose
NHANES	National Health and Nutrition Examination Survey
nM	nanomole
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NTP	National Toxicology Program
OP	organophosphorus compound
OPP	Office of Pesticide Programs
PAD	population adjusted dose
2-PAM	pralidoxime
PFC	plaque-forming cells
Pb	lead
pbB	blood lead concentration
PBPK	physiologically based pharmacokinetic
PBPK/PD	physiologically-based pharmacokinetic/pharmacodynamic
ppb	parts per billion
ppm	parts per million
RfC	reference concentration
RfD	reference dose
sc	subcutaneous
TCP	3,5,6-trichloro-2-pyridinol
TTD	target-organ toxicity dose
µg	microgram
µmole	micromole
U.S.	United States
VOC	volatile organic compound
WHO	World Health Organization
WOE	weight-of-evidence
ZPP	zinc protoporphyrin

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to